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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,560	02/22/2000	Kenneth Iain Cumming	00.1090.US	3011

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/510,560	CUMMING ET AL.	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *110-177* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *110-177* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application and Claims

A Request for Continued Examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on September 14, 2006, has been entered.

Applicants have canceled claims 96 and 97. Claims 110-177 are pending in the instant application and are the subject of the Office Action below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 110-177 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

Claims 110-177 are indefinite for reciting the term "macromolecular" because one of ordinary skill in the art could not reasonably be able to determine metes and bounds of this limitation. Neither the specification nor the art provides a definition that allows one or ordinary skill in the art to distinguish those compounds considered to be macromolecular from compounds that are not macromolecular. For example, a molecular weight range is not set forth in the specification, nor is the term "macromolecular" or "macromolecule" explicitly defined by size or molecular weight. The selective dictionary definition provided by Applicants is for the phrase "macromolecular chemistry," and is therefore not on point with the instant term. In contrast, the *McGraw-Hill Dictionary of Chemical Terms* does not limit either the terms "macromolecular" or "macromolecule" to compounds having a molecular weight of 1000 (page 251). Correction is required.

Claims 110-177 are indefinite for reciting the term "hydrophilic" because one of ordinary skill in the art could not reasonably determine metes and bounds of this limitation. Neither the specification nor the art provides a definition that allows one or ordinary skill in the art to distinguish those compounds considered to be hydrophilic from compounds that are not hydrophilic. The *McGraw-Hill Dictionary of Chemical Terms* defines the term hydrophilic as "[h]aving and affinity for, attracting, adsorbing, or absorbing water" (see page 209) which is inadequate for the purposes of claim construction since this term is subjective to those of skill in the art, unlike a more definitive measure with a defined threshold, such as a partition coefficient. Correction is required.

Claim 173 is indefinite because the claim is presented as having an improper Markush group. It is not clear if Applicants are requiring a single member from (a) *and* (b), or just one member from (a) *or* (b).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 110-113, 118-131, 133, 134, 136-147, 152-164, 166, 167 and 169-177, are rejected under 35 U.S.C. § 102(b) as being anticipated by Bachynsky *et al.*, Irish Patent No. (11) 63119, published on March 22, 1995, and Bachynsky et al., U.S. Patent No. 5,190,748, issued on March 2, 1993.

Applicants arguments in response to the previous rejection over Bachynsky:

Applicants allege that Bachynsky does not anticipate certain elements of the claimed invention because Bachynsky teaches a non-macromolecule active compound, and that Laureth-12 is not a solid at room temperature. Applicants' arguments have been fully considered, however, are not persuasive for the reasons below.

As explained above, ceftriaxone meets the definition of "macromolecule" because it is a "large" molecule, and/or "hydrophilic" molecule (see captioned definition above for hydrophilic).

Regarding Applicants' contentions that Laureth-12 is not a solid at room temperature, this is false. The selective evidence provided by Applicants appears to relate to the state of Laureth-12 at high temperatures; the MSDS for Lumulse L-12 describes Laureth-12 at high temperatures, such as 200 °C. However, the technical data sheet (TDS)[1] provided in a hyperlink alongside the MSDS hyperlink from one of Lambent Technologies' webpages,[2] clearly describes Lumulse L-12 as a solid at 25 °C (Technical Data Sheet, page 2). Accordingly, Bachynsky does teach the claimed limitations.

Comparison of claims to disclosure of Bachynsky:

Claim 110, 142, 143, 144, 153, 174, are directed to a composition comprising a blend of a hydrophilic drug or macromolecular drug, a an enhancer, wherein the enhancer is a salt of a medium chain fatty acid, and the enhancer and composition are solids at room temperature.

Bachynsky teaches a blend of a "macromolecular"/"hydrophilic" drug (*i.e.*, ceftriaxone), and a salt of a medium chain fatty acid having a carbon chain length of from 6 to 20 carbon atoms (*i.e.*, sodium caprylate), with optional constituents Laureth-12 and Witepsol™ H15 (the '748 patent, col. 12, lines 59-65). Therefore, Bachynsky also metes the enhancer limitations of claims 111-113, 141, 145-147 and 173. The blend, as well as each of the drug, medium chain fatty acid salt, and the other constituents, each are solids at room temperature. The blend is capable of forming an oral dosage form (such as claims 120, 143 and 153), and the sodium caprylate would serve as an enhancer. Bachynsky also quite clearly teaches another formulation comprising sodium caprylate as and enhancer with ceftriaxone:

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[1] Lambent Technologies: Technical Data Sheet for LUMULSE L-4, LUMULSE L-12 and LUMULSE L-23.

> "Absorption was also evaluated using a formulation composed of 300 mg of ceftriaxone sodium salt, 200 mg of sodium caprylate, 75 mg of Laureth-12 and 415 mg of Witepsol H15."

Bachynsky, col. 13, lines 14-21. Bachynsky also teaches a compressed tablet or pill:

> "The preferred method of orally administering the combination of antibacterial compound and absorption enhancing system in accordance with this invention is in the form of an enteric coated entity, and more specifically, an enteric coated solid dosage form. The formulation can be filled into a hard- or soft-shell capsule or, if the formulation is a liquid, absorbed onto a suitable carrier to make a free flowing powder and then filled into the capsule or, alternatively, *compressed* into a pill or *tablet*. Still other possible dosage forms include microcapsule or beadlet forms of the antibacterial compound mixed with the absorption enhancing system which may thereafter be encapsulated in an enteric coated capsule."

Bachynsky, col. 8, lines 13-27 (emphasis added). Accordingly, claim 175 is anticipated. As in claims 176 and 177, a therapeutically effective amount of the active is used for treatment of infection (col. 1, lines 10-21).

This formulation is formed in a hard shell gelatin capsule, and therefore metes the limitations of claims 121, 133, and 166.

Further, the capsule has an enteric coating (col. 8, lines 18-26), such as polyvinyl acetate phthalate (col. 12, lines 65-66), or methacrylic acid and its ester (col. 8, lines 45-46), which are "rate controlling" and "delays release", and therefore metes the limitations of claims 122, 125, 127, 128, 134, 137, 140, 155, 158, 160, 161, 167, and 170. Since Bachynsky teaches an enteric coated tablet, the tablet is effectively multilayered (claims 124, 129, 138,139, 157, 171 and 172).

Bachynsky teaches tablets and beadlets (*i.e.*, metes the limitations of either particles or pellets), and therefore meets the limitations of claims 123, 130, 131, 136, 154, 156, 162, 163, 164, 169.

As in claims 126 and 159, Bachynsky discloses HPMC, which is "rate controlling" (col. 8, lines 60-66).

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[2] see document labeled Appendix A: Webpage publication provided by Lambent Technologies – found online at www.petroferm.com/prodinfo.asp?bus=2&mkt=4&app=3, on December 5, 2006.

Claims 118 and 152 are directed to the ratio of the drug to enhancer in the range of 1:100,000 to 10:1; the ratio of the drug to enhancer taught by Bachynsky is 0.3:1 to 1.5:1 (see table, page 14, lines 15-19).

Claims 110, 114, 116, 117, 119 and 176, are rejected under 35 U.S.C. § 102(b) as being anticipated by Fujii et al., U.S. Patent No. 5,840,685, issued on November 24, 1998.

Fujii teaches the administration of heparin (paragraph bridging col. 2 and 3) and LH-RH (col. 5, lines 41-60) and sodium caprylate (i.e., solid) as an enhancer in the form of a tablet (*i.e.*, solid; col. 7, lines 10-25). Fuji states the following with regard to absorption promoters:

> "Preferred medium chain aliphatic carboxylic acids are sodium caproate, *sodium caprylate*, sodium caprate and sodium laurate. The most preferred medium chain aliphatic carboxylic acid salt is sodium caprate."

Fujii, col. 6, lines 30-37 (emphasis added).

Accordingly, claims 110, 114, 116, 117, 119 and 176 are anticipated.

Claims 110-131, 133, 134, 136-164, 166, 167, and 169-177, are rejected under 35 U.S.C. § 102(b) as being anticipated by Watts et al., International Patent Application Publication WO 97/05903, published on February 20, 1997.

The limitations of claims 110-113, 118-131, 133, 134, 136-147, 152-164, 166, 167 and 169-177, are detailed above, and hereby incorporated into the instant rejection.

Watts discloses a drug delivery composition (tablet, capsule, including a gelatin capsule, and a pellet) for colonic delivery through oral administration (see Abstract; accordingly this is a delayed release formulation) comprising a drug (e.g. polypeptide and polysaccharide including heparin and low molecular weight heparin; see page 8), and an absorption promoter (see page 24), such as low molecular weight heparin (see Example 10 on page 22; heparin further meets the limitations of claims 114-117 and 148-151). This formulation is a solid at room temperature, as is the enhancer, and is provided as a capsule. It is also provided with the auxiliary excipient Labrasol. Watts teaches that the absorption promoter comprises a fatty acid or a salt thereof, where the fatty acid has between 6 and 16 carbon atoms, for example capric acid (Example 10) or its (sodium) salt (e.g. se pages 5, 24, claims 1 and 3) which can be used *alone* or in admixture

with a fatty acid derivative (e.g. mono/diglycerides: see pages 5-7) to obtain synergy. Watts further teaches that the drug can be chosen from insulin, calcitonin, LHRH, buserelin, goserelin, vasopressin, heparin, and more (p 8, 11-12, and p 24, claim 6). Watts teaches that the composition is formulated in a capsule (e.g. hard/soft gelatin), tablet, pellet, or multiparticulate capsule or tablet which is comprised of or coated with a material which is dissolved by the conditions found in the intestines e.g. "rate-controlling" (e.g. sustained release), such as a cellulose ester, HPMC (e.g. see page 9, lines 14-29) or a methacrylic acid polymer (pages 10-12) for in vivo therapeutic administration to a patient (see pages 14-15). In Example 10 (page 22), Watts teaches:

> "Into a glass vial was weighed 875 mg of LABRASOL™ and 875 mg of capric acid. The vial contents were heated to 40 °C. until the capric acid has dispersed. 1741 mg of low molecular weight heparin (LMWH. 145 IU/mg) was added to the melted LABRASOL.TM./capric acid mixture. Into each of eight starch capsules was weighed 349 mg of the mixture, equivalent to 174 mg of LMWH, 87.5 mg LABRASOL.TM. and 87.5 mg capric acid. Each of four pigs weighing approximately 65 kg was administered two of the capsules into the ileal fistula as described in Example 1. As controls, each pig was administered two starch capsules containing 174 mg of LMWH powder. . Plasma samples were collected and the anti-factor Xa activity measured using a proprietary assay kit. By measuring the anti-factor Xa activity in standards containing known quantities of LMWH. tile LMWH content of the pig plasma samples was calculated. The plasma LMWH concentration vs. time profiles for the enhancer and control formulations are shown in FIG. 10. The formulation containing LABRASOL.TM. and capric acid was effective in enhancing colonic absorption of LMWH."

Watts, page 22.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 110-134, 136-167, and 169-177, rejected under 35 U.S.C. § 103(a) as being unpatentable over Watts, in view of Mulqueen et al., U.S. Patent No. 6,017,559, issued on January 25, 2000.

The limitations of claim 110-131, 133, 134, 136-164, 166, 167, and 169-177, as well as the corresponding teachings of Watts, are set forth above and are hereby incorporate by reference.

Claims 132 and 165 are directed to two or more populations of particles, which is not explicitly stated by Watts.

Mulqueen teaches a method for preparing microcapsules with bimodal and multimodal distributions that are solids and may be used to be placed in finished capsules. Mulqueen states:

> "It is very difficult by conventional methods to produce emulsions with particle sizes and particle size distributions which are both easily reproducible, and easily controlled. By contrast, many of the templating agents which can be employed in accordance with the present invention can easily be produced in particle size distributions which are easy to control, and in particular which have a narrow particle size distribution, or which have a multimodal (e.g., a bimodal) particle size distribution."

Mulqueen, paragraph bridging cols. 1 and 2; and:

> "The non-aqueous phase employed in the production of such microcapsules may contain chosen amounts of plasticizer for the wall of the finished capsule, thus enabling control of the release kinetics of the finished microcapsules."

Mulqueen, col. 5, line 59-62.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Watts and Mulqueen are directed to the

pharmaceutical arts. While Watts is primarily focused on providing certain peptide based therapeutics in the presence of an enhancer, Watts certainly recognizes the variety of pharmaceutical formulation considerations and forms that may be applied depending on the therapy, including tablets and capsules, as well as various controlled/delayed release formulations. Mulqueen provides a solution for improved production control of certain pharmaceutical forms, namely, controlled size microsphere production. Mulqueen states that his invention is useful in the production of multimodal size distributions of microspheres, which he suggests have the advantage of providing the a range of delivery rates for the pharmacologists intended delivery profile. Therefore, the invention as whole is *prima facie* obvious over the art of record.

Claims 110-134, 136-167, and 169-177, rejected under 35 U.S.C. § 103(a) as being unpatentable over Watts, in view of Getz et al., U.S. Patent No. 6,270,804, issued on August 7, 2001.

The limitations of claim 110-131, 133, 134, 136-164, 166, 167, and 169-177, as well as the corresponding teachings of Watts, are set forth above and are hereby incorporated by reference.

Getz is directed to a method of providing pharmaceutical solutions in the physical form of a sachet. Getz teaches that bioaffecting sachets, or powders, containing coated liquiflash microspheres and partially recrystallized shearform floss particles are disclosed. The sachets give organoleptically acceptable properties, including a pleasing mouthfeel, when orally ingested, including actives such as insulin and LH-RH (see *Summary of the Invention*, and cols. 3-5).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Watts and Getz are directed to the pharmaceutical arts. While Watts is primarily focused on providing certain peptide based therapeutics in the presence of an enhancer, Watts certainly recognizes the variety of pharmaceutical formulation considerations and forms that may be applied depending on the therapy, including tablets and capsules, as well as various controlled/delayed release

formulations. Getz provides certain solutions via sachets, and teaches that sachets have certain advantages over tablet or capsule forms, such as improved mouthfeel for some patients.

Conclusions

No claims is allowable.

Also related to the claimed invention is the disclosure Andriuoli *et al.*, *Haemostasis 20(suppl 1)*:154-158 (**1990**); and Lindmark *et al.*, *J. Pharm. Ex. Therapeutics275(2)*:958-964 (**1995**).

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

12/11/06
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PATENT EXAMINER